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1627	18

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/351,617	Applicant(s) Mehta et al
	Examiner Padmashri Ponnaluri	Art Unit 1627

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Dec 20, 2001* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 6, 12-20, 23, 24, 26, 27, and 31-35* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 6, 12-20, 23, 24, 26, 27, and 31-35* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/20/01 has been entered.

2. The amendment C, filed on 12/20/01 cancels claims 21-22 and adds new claim 35.

3. Claims 1, 6, 12-20, 23-24, 26-27, 31-35 are currently pending in this application.

4. The oath or declaration is defective. **A new oath or declaration in compliance with 37CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.**

The oath or declaration is defective because:

It was not executed in accordance with either 37 CFR 1.66 or 1.68.

The oath or declaration filed on 3/23/01 fails to include all the inventors (does not identify all the inventive entity).

Applicants assertion that two declarations (one filed on 3/23/01 **with only one inventor**; and the other declaration filed on 9/17/99 has listed all the inventors, however **the declaration**

has altered address of the inventor without initials) provide all required data under 37 C.F. R 1.63 is not persuasive, because **Rule 1.67, (a), (2), states that** .. "*deficiencies or inaccuracies relating to fewer than all of the inventor(s) or applicants ...may be corrected with a supplemental oath or declaration* ***identifying the entire inventive entity*** *but signed by only one inventor(s) or applicant(s) to whom the error or deficiency relates.*"

Applicants are requested to file a new/ supplemental oath/declaration according to Rule 1.67.

5. Applicant is invited to notice that boxes 5, 10 and 12 were checked by the draftsman. If applicants renumber the figures, applicant is encouraged to amend the specification so that the description of renumbered figures corresponds to the renumbered figures.

6. The new matter rejection of claim 33 (in the previous office mailed on 6/20/01) has been withdrawn in view of applicants response.

7. Applicant's arguments with respect to claims 1, 6, 12-20, 23-24, 26-27, 31-35 have been considered but are moot in view of the new ground(s) of rejection.

8. Claims 1, 31 an d35 are objected to because of the following informalities: the claims include 'covalnet' in brackets. Bracketing is commonly used to indicate amendments or changes

in the claims as provided in 37 CFR 1.121(a)(2)(ii) and are normally not intended to be printed in the published patent. The use of the brackets is unclear because whehter applicants intend that the bracketing to appear in the claims in the published patent, such intention must be clearly indicated.

Appropriate correction is required.

Claim Rejections - 35 U. S. C. § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1, 6, 12-20, 23-24, 26-27, 31-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, and 35 are indefinite by reciting 'small molecule'. It is not clear what does applicants mean by 'small molecule' which is a relative term. The specification does not disclose any definition for 'small molecule' or does recite the limitations of size of small molecule (i.e, less than ....Daltons is considered as small molecule).

Claim 31 recites, 'pharmacologically relevant small molecules' clarification is requested what does applicants mean by 'pharmacologically relevant small molecule'. The specification does not give examples or definition for the limitation. Applicants are requested to clarify.

Claims 1 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: showing that the bond between hybrid ligand A and the predetermined target is a irreversible (covalent) bond. The claims are missing an essential element which shows that the bond between the ligand A and the predetermined target is irreversible. The specification does not show that the bond is irreversible or how to determine that the bond is irreversible.

Claims 1, 31 and 35 recite 'irreversible (covalent) bond'. However, the specification does not disclose what is 'irreversible (covalent bond).' The specification does not disclose affinities or Kd values for complex formation, to show that the interactions are 'irreversible (covalent bond).

Claim Rejections - 35 U.S.C § 102 and 35 U.S.C § 103

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1, 6, 12, 17, 19, 20, 23-24, 31-32, 35 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Licitra et al (Proc. Natl. Acad. Sci. USA., vol. 93, pp. 12817-12821, November 1996) (cited by applicants in the PTO-1449, filed on 12/9/99).

The instant claims are drawn to a method and a kit of reagents (claim 31) for identifying a cellular component to which a small molecule is capable of binding, comprising: providing a hybrid ligand having ligands A and B; wherein ligand A forms a covalent bond with a predetermined target, and ligand B is small molecule; introducing the hybrid ligand into a sample

containing: (I) a first expression vector encoding a first hybrid protein comprising the target of ligand A and a first transcriptional module, (ii) a second expression vector encoding a second hybrid protein comprising the a random DNA fragment encoding a polypeptide and a second transcriptional module, (iii) a third vector including a reporter gene, and the reporter gene is expressed when the first and second proteins are in proximity; permitting the hybrid molecule to bind covalently the first hybrid protein through the ligand A and the second hybrid protein through ligand B so as to activate the expression of the reporter gene; identifying the samples expressing the reporter gene; and characterizing the second hybrid protein in the samples so as to determine the cellular component to which small molecule has a binding affinity.

Licitra et al disclose a three-hybrid system (method) for detecting small ligand-protein receptor interactions in vivo (see the abstract). The reference discloses that the method comprises a synthetic 'bait' hybrid ligand (hybrid ligand of the instant claims) comprising dexamethasone (refers to ligand A of the instant claims) and FK 506 (refers to ligand B of the instant claims; and instant claim 19 (small molecule has a known function)) (see the abstract and diagram 2, in page 12819). The reference discloses that the hybrid ligand was introduced to a yeast strain (EGY48) expressing fusion proteins (refers to hybrid proteins of the instant claims) 'hook fusion protein' and 'fish fusion protein', wherein the hook fusion protein has a hormone binding domain of rat glucocorticoid receptor (receptor for ligand A) fused to LexA DNA binding domain (refers to transcriptional module of the instant claims and instant claim 12); and the fish fusion protein has FKBP12 (receptor for ligand B) fused to a transcriptional activation domain of a transcriptional

factor (refers to second transcriptional module of the instant claims and instant claim 12). The 'fish', and 'hook' proteins (fusion proteins) and bait hybrid ligand form the three hybrid molecules. The reference discloses that when the ligand A binds to its receptor fused to a DNA binding domain of the 'hook fusion protein; and ligand B binds to its receptor fused to a transcriptional activation domain of the 'fish fusion protein' the reporter genes are activated allowing for the selection of the yeast cells that harbor the relevant receptors (see page 12819, left column, and also the diagram 2) (refers to steps (b) - (e) of claim 1 of the instant claims). The reference discloses that the disclosed method of three hybrid system has advantages over known biochemical methods for identifying receptors for small ligands , and the method will also be useful for generation of high affinity binding proteins to small ligands such as environmentally hazardous compounds or drugs. The reference also discloses that the three hybrid system can also be applied to screen for novel ligands for a given receptor both in yeast and in mammalian cells in vivo (refers to instant claim 6). The reference discloses that with the availability of synthetic combinatorial libraries of small organic molecules, the system offers highly efficient way to identifying such ligands (see page 12820, right column) (refers to instant claims 20 and 23). The reference also discloses that in the case of receptor with no known ligand it is conceivable that a hybrid combinatorial library of covalently linked to a known ligand such as dexamethasone can be screened to discover new lead compounds for drug development. The reference discloses that the DNA fragment encoding a polypeptide of the second expression vector is from a cDNA library (i.e, see figure 4, and page 12820, left column) (refers to random DNA fragment of the

instant claims). The reference discloses that the second vectors (fish vectors) from the colonies which were completely inhibited by the FK506 (ligand B) were retrieved and sequenced the cDNA inserts (refers to step (e) of the instant claims).

The claimed invention further differs from the prior art teachings only by the recitation of formation of irreversible (covalent) bond with the predetermined target. The reference teaches the three hybrid system "hook-bait-fish" in which the bait has 'A' and 'B' components linked by a linker, in which 'hook' is consists of receptor for 'A' component of the bait. The reference teaches that ligand 'A' binds to the receptor fused to a DNA binding domain (the hook). The reference does not teach the binding of the ligand 'A' to the target is 'irreversible'. The reference teaches all the method steps of the instant invention. The claimed invention does not differentiate or point out how the bond between the ligand A and the target is irreversible, or the formation of the 'irreversible bond' between the ligand A and the target results in a method, which is different from the prior art method. In the absence of further teachings in the specification, the claimed invention appears to be the same or obvious variations of the reference teachings, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to determine and/or compare the specific activities of the instant versus the reference method. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed method is different from the one taught by prior art and to establish the patentable differences. See in re Best 562F.2d 1252, 195 U. S. P. Q. 430 (CCPA 1977) and Ex parte Gray 10 USPQ2d 1922(PTO Bd.Pat. App. & Int. 1989).

Claim 31 is included in this rejection because, it would be obvious to skilled in the art at the time the invention was made to formulate and dispense the reagents used in the three hybrid system in a kit of ease of use.

14. Claims 1, 6, 12, 17, 19, 20, 23-24, 31 and 35 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over US Patent 5,928,868 (Liu et al) (cited by applicants in the PTO-1449, filed on 12/9/99).

Liu et al disclose a three hybrid screening assay. Liu et al disclose methods and kit for characterizing small molecules from a library of small molecules or alternatively identifying a protein targets to which known small molecules bind (see abstract). The reference method includes forming a hybrid ligand in which at least one molecule is a small molecule. (See the abstract). The hybrid ligand is introduced into cells that in turn contain a first and second expression vector containing DNA for expressing a hybrid protein and a transcriptional module, and a third vector with a reporter gene, expression of which is conditioned on the proximity of the first and second hybrid proteins (see abstract). The reference discloses that the three hybrid system involves the formation of a complex between a hybrid ligand and two hybrid proteins in which one component of the complex is unknown, and the unknown component in the assay may be either small molecule contained in the hybrid ligand or one of the hybrid proteins (see column 5, lines 16-21). The reference discloses that the utility of the assay include determining the identity of a target molecule having a binding affinity with a known small molecule where the

small molecule has a pharmacologic activity and the target may be suited for therapeutic intervention in a variety of diseases (see column 5). The reference method discloses that the hybrid ligand comprises a small molecule (refers to ligand B of the instant claims) and a known molecule (refers to ligand A of the instant claims), and the known molecule binds to a known second target (refers to predetermined target; and the covalent bond of the instant claims) (see claim 1, step (a)). The reference discloses that the hybrid ligand is introduced into cell containing a first expression vector containing a DNA encoding a first known target, linked to a coding sequence of a first transcriptional module for expression as first hybrid protein; a second expression vector containing DNA fragment encoding a polypeptide linked to a transcriptional module for expression as a second hybrid protein ; and a third vector containing a reporter gene (refers to the step (b); and the cells refer to the environment of the instant claims) (see i.e., claims 1 and 17, step (b)). The reference discloses that the hybrid ligand binds to the first hybrid protein and the second hybrid protein so as to activate the expression of the reporter gene (refers to step © of the instant claims (i.e., see claim 1 , step (c)); and claim 17, steps (d) and (e) of the reference method refers to steps (d) and (e) of the instant claims. The reference discloses that the random fragment of second vector are selected from genomic DNA, cDNA, synthetic DNA or from a plurality of libraries (i.e., see claims 20-21) (refers to instant claims 14- 15). The reference discloses that the cDNA is derived from an immune cell, or from an immune cell capable of producing an immune response to ligand B (refers to small molecule contaminant) (i.e., see claims 22-23) (refers to instant claims 16-17). The reference discloses that the ligand B

has a known biological function (i.e., see claim 24) (refers to instant claim 19). The reference discloses that the cells are mammalian cells (see i.e., claims 6, 29) or yeast cells (see i.e., claims 5, 28), or the lysates (see i.e., claim 4) (refers to instant claim 6 of the instant claims). The reference discloses that the transcriptional modules are selected from DNA binding protein and a trascriptional activator (i.e., see claim 10), and the small molecule is obtained from a combinatorial library of small organic molecules (see i.e., claims 12-13) (refers to instant claims 20 and 23). The reference discloses that the small molecule is an environmental contaminant (see claim 14) (refers to claim 24 of the instant claims). The reference method further disclose that the method steps (b) to (e) are repeated in the presence of random small molecules for the competitive binding with the hybrid ligand (see i.e, claim 16) (refers to instant claim 27). The reference discloses that a random DNA sequences of a size that is capable of encoding undetermined target protein may be inserted in the second expression vector where the random DNA sequences are derived from a genomic DNA library, cDNA library or synthetically generated library from eukaryotic cells, prokaryotic cells, viruses or formed by an automated DNA synthesizer (i.e., see column 8, lines 2-8). The reference discloses a kit for detecting interactions between the pharmacologically relevant small molecules and proteins comprising: (a) a hybrid ligand; (b) a first expression vector; © a second expression vector; (d) a third vector; (e) an environment for transcription and translation; and (f) a means for detecting the expression of the reporter gene (see i.e., claim 18) (refers to instant claim 31).

The claimed invention further differs from the prior art teachings only by the recitation of formation of irreversible (covalent) bond with the predetermined target. The reference teaches three hybrid system 'hook-bait-fish' in which 'bait' has 'A' and 'B' components linked by a linker. The 'hook' consists of a receptor for 'A' component of the 'bait'. The reference teaches that ligand 'a' binds to the receptor fused to a DNA binding domain. The reference teaches all the method steps of the instant invention. The claimed invention does not differentiate or point out how the bond between the ligand A and the target is irreversible, or the formation of the 'irreversible bond' between the ligand A and the target results in a method, which is different from the prior art method. In the absence of further teachings in the specification, the claimed invention appears to be the same or obvious variations of the reference teachings, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to determine and/or compare the specific activities of the instant versus the reference method. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed method is different from the one taught by prior art and to establish the patentable differences. See in re Best 562F.2d 1252, 195 U. S. P. Q. 430 (CCPA 1977) and Ex parte Gray 10 USPQ2d 1922(PTO Bd.Pat. App. & Int. 1989).

15. No claims are allowed.

16. The lengthy specification has not been checked to the extent necessary to determine the

presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Any inquiry concerning this communication should be directed to P. Ponnaluri whose telephone number is (703) 305-3884. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat, can be reached at (703)308-2439. The fax number for this group is (703)305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist whose telephone number is (703)308-0196.

P. Ponnaluri
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Art Unit 1627
6 March 2002

PADMASHRI PONNALURI
PRIMARY EXAMINER